Editorial Commentary

Dose-dense adjuvant chemotherapy for high-risk early breast cancer: its role in the era of personalised oncology

Constantinos Savva^, Ramsey Cutress, Ellen Copson

School of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Correspondence to: Dr. Constantinos Savva, MD, MSc, PhD, MRCP. School of Cancer Sciences, Faculty of Medicine, University of Southampton, Tremona Road, Southampton SO16 6YD, UK. Email: c.savva@soton.ac.uk.

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The PANTHER trial is a phase III multicentre randomised clinical trial, aimed to evaluate the efficacy of dose-dense versus standard adjuvant chemotherapy in early high-risk breast cancer (EHRBC) (1). The final efficacy analysis is now presented in the *Journal of Clinical Oncology* after a median follow-up of 10.3 years. The trial recruited 2017 women aged 18–65 years, who had undergone primary surgery for EHRBC across Sweden, Germany, and Austria between February 2007 and September 2011. The study included patients with hormone receptor-negative or positive tumours with one or more positive axillary lymph nodes, axillary node negative breast cancers if the primary tumour was larger than 20 mm and receptor negative with a histological grade 3, or patients 35 years or younger with primary breast cancer of any biological subtype and axillary nodal status that were considered suitable for adjuvant chemotherapy. Dose-dense chemotherapy, as reported here, involves reducing the interval between successive treatments compared to a standard regimen at the same total dose and number of cycles.

The primary endpoint analysis, published in 2016, showed a 4.6% improvement in 5-year event-free survival (EFS) with dose dense chemotherapy with no difference in the overall survival (OS) between dose-dense and control groups (2). Additionally, a subgroup analysis of the 10-year follow-up, published in 2025, showed an improvement in breast cancer recurrence-free survival (BCRFS) across all subgroups supporting the use of dose-dense chemotherapy in all patients with primary resected EHRBC (3).

The primary outcome of the PANTHER trial was BCRFS, defined as time from randomization to the first local-, regional- or distant breast cancer recurrence or death due to breast cancer or last date of follow-up if no event has occurred. Patients in the dose-dense group received epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) (EC) once every 2 weeks for four cycles, followed by four cycles of docetaxel (75 mg/m^2) once every 2 weeks. Dose tailoring was performed according to a predefined algorithm based on hematologic and nonhematologic adverse events. The control group received fluorouracil (600 mg/m^2) epirubicin (75 mg/m^2) and cyclophosphamide (900 mg/m^2) (FEC) every 3 weeks for three cycles, followed by docetaxel (75 mg/m^2) once every 3 weeks for three cycles, dosed conventionally by body surface area. All patients received radiotherapy and endocrine treatment according to national and local guidelines., and human epidermal growth factor receptor-2 (HER2) positive patients received adjuvant trastuzumab.

The PANTHER trial provides valuable insights into the benefits of tailored dose-dense chemotherapy. Previous studies on dose-dense approaches have shown some inconsistent results, but the Early Breast Cancer Trialists'

^ ORCID: 0000-0003-0805-4719.

Collaborative Group (EBCTCG) meta-analysis reported that regimens with higher cumulative doses of anthracycline plus taxane offer the greatest survival benefit, indicating that cumulative dose is crucial regardless of the interval (4).

The PANTHER study showed that the use of dose-dense chemotherapy was associated with a 20% improvement in BCRFS, a 22% improvement in EFS, defined as time from randomization to the first of the events breast cancer recurrence of any type, contralateral breast cancer, other malignancy or any cause of death, and a 21% improvement in distant disease-free survival (DDFS) [hazard ratio (HR) 0.80, 95% confidence interval (CI): 0.65–0.98; HR 0.78, 95% CI: 0.65–0.94; HR 0.79, 95% CI: 0.64–0.94, respectively] compared to the standard adjuvant chemotherapy group. Additionally, the PANTHER trial indicated a 1.5% absolute increase in 10-year OS with dose-dense chemotherapy (16.6%) compared to the control arm (15.1%), although this difference was not statistically significant (HR 0.82, 95% CI: 0.65–1.04). Thus, while the PANTHER trial demonstrates a clear benefit in reducing disease recurrence compared to standard 3-weekly docetaxel chemotherapy, a more effective taxane, the impact on OS remains uncertain. This modest difference may still inform clinical discussions about treatment intensity.

The PANTHER trial is characterised by several strengths including its large sample size and long follow-up period, providing robust evidence for the efficacy of dose-dense chemotherapy in EHRBC. Patient characteristics were well-balanced between the two treatment groups, minimising bias. The study utilized an optimal control regimen of docetaxel once every 3 weeks, addressing limitations of previous trials that used a suboptimal control regimen of paclitaxel every 3 weeks. In the tailored dose-dense chemotherapy and standard chemotherapy groups, 80.4% and 79.3% of the patients had oestrogen receptor or progesterone receptor positive, 84.0% and 81.8% had HER2 negative disease, 62.1% and 58.4% had less than four positive lymph nodes, respectively. Relapses occur at a later stage for the majority of the patients with these clinicopathological characteristics (5).

The main confounder in this study is the impact of cumulative chemotherapy dose and a higher number of chemotherapy cycles. The experimental group received eight cycles, while the control group received six. The study mentions that the differences in median cumulative chemotherapy doses were below clinically relevant thresholds established by the latest EBCTCG meta-analysis (6). Additionally, the outcomes in the dose-dense group were not associated with cumulatively higher epirubicin doses. A more detailed analysis exploring the relationship between cumulative dose and treatment outcomes would strengthen the conclusion that the dose-dense schedule, rather than just the higher cumulative dose, drives the observed benefits.

No new safety concerns were reported in the PANTHER trial. However, the dose-dense group was associated with a higher discontinuation rate, mainly attributed to treatment toxicity (109/174) compared to the control group (34/60), suggesting that dose-dense chemotherapy is less tolerable. Acute side effects were reported in the original publication of the trial, with higher non-haematological side effects in the experimental group compared to the control group (52.6% *vs.* 36.6%) (2). Long-term toxicities, such as secondary cancers, were comparable in both groups; however, the risk of cardiomyopathy was not reported (2).

The PANTHER trial primarily focuses on survival outcomes such as BCRFS, EFS, and DDFS. A more comprehensive evaluation of long-term side effects and their impact on patients' quality of life would provide a more complete picture of the risks and benefits of dose-dense chemotherapy. Furthermore, at the end of the study there were 137 deaths in the dose-dense arm and 166 in the standard of care arm. Although the average adjusted 30-day mortality post-chemotherapy for early breast cancer is low at 2.7% (7), it would be important for clinicians to know the proportions of chemotherapy-related deaths in each treatment group. Furthermore, time to recover from chemotherapy toxicities, especially in the dose-dense group, is also important as this may impact the quality of life of these patients (8). In the neoadjuvant setting, dose-dense chemotherapy not only did not improve complete pathological response rate, but it was also associated with delayed surgery due to prolonged side effects such as neutropenia and thrombocytopenia (9). These data would help clinicians make more informed treatment decisions and enable patients to better understand the potential acute and long-term consequences of this intensive treatment approach.

Subgroup analysis in the PANTHER trial showed a 22% (HR 0.78, 95% CI: 0.62–0.99) lower risk of BCRFS in oestrogen receptor-positive patients and 47% (HR 0.53, 95% CI: 0.30–0.93) lower risk in HER2-positive patients. However, there was no statistically significant difference in BCRFS in patients with oestrogen receptor-negative or HER2-negative breast cancer. Dose-dense chemotherapy was also associated with improved BCRFS in women older than 50 years (HR 0.74, 95% CI: 0.56–0.97). There was

also a significant amount of missing data for the Ki-67 proliferation index, a prognostic in breast cancer. A more complete dataset on Ki-67 would allow for a more thorough analysis of its potential impact on treatment outcomes and could enhance the understanding of the study's findings. This suggests that the use of adjuvant dose-dense chemotherapy may have a survival benefit compared to the standard of care in certain subtypes of breast cancer.

The increased use of neoadjuvant chemotherapy combined with immune checkpoint inhibitors for triple-negative breast cancer (TNBC) and dual anti-HER2 blockade for HER2-positive breast cancer has significantly impacted surgical approaches and survival outcomes (10,11). Achieving a complete pathological response with these treatments helps tailor additional therapy for patients who do not reach this milestone, optimizing their overall treatment plan (10,11). Additionally, response-adapted adjuvant therapy has shown significant survival benefits. Using trastuzumab emtansine for HER2-positive breast cancer and adjuvant olaparib for selected germline breast cancer gene (BRCA) 1/2 mutation carriers with HER2-negative breast cancer and residual invasive cancer post-neoadjuvant chemotherapy improved 7-year survival by 4.7% and 4-year survival by 3.4% compared to the control group, respectively (12,13). A large observational study, investigating immunotherapy integration in neoadjuvant treatment for TNBC suggest a trend towards increased pathological complete response and grade 3 toxicities with dose-dense chemotherapy, particularly in stage III disease, that was non-statistically significant (14). These findings underscore the need for randomized controlled trials to evaluate the benefits of dose-dense neoadjuvant chemoimmunotherapy.

Adjuvant treatment of oestrogen receptor-positive HER2-negative breast cancer has evolved since the design of the PANTHER study. Advances in molecular profiling scores to assess recurrence risk, such as Oncotype DX, MammaPrint, and Prosigna, allow for personalized treatment recommendations for adjuvant chemotherapy and therefore a reduction in its use, particularly in the postmenopausal population (15). For this reason, adjuvant chemotherapy is now recommended for clinically or genomically high-risk oestrogen receptor positive/HER2 negative breast cancer (15). For these patients, dose-dense chemotherapy may still be a considered to reduce the risk of recurrence. Furthermore, optimisation of endocrine therapy with increased use of ovarian suppression in young patients as well as the more recent use of adjuvant abemaciclib or ribociclib, cyclin dependent kinase inhibitors, has revolutionised the treatment landscape for high-risk oestrogen receptor-positive/HER2-negative breast cancer (16). These therapies offer less toxic alternatives and they may reduce the need for dose-dense chemotherapy, especially in patients with low to moderate recurrence risk.

Molecular profiling, and specifically sensitivity to endocrine therapy, was used to identify patients who benefit most from dose-dense chemotherapy in the C9741 trial (17). The 12-year follow-up of the C9741 trial confirmed the benefit of dose-dense chemotherapy for node-positive breast cancer, demonstrating a 23% improvement in disease-free survival (HR 0.77, 95% CI: 0.66–0.90) and a 20% improvement in OS (HR 0.80, 95% CI: 0.67–0.95) in the whole cohort that included both oestrogen receptor-positive and negative patients (17). The study identified the SET2,3 index, a genomic test for endocrine transcriptional activity, as a predictive factor of survival in oestrogen receptor-positive patients. Dose-dense chemotherapy significantly improved survival compared to conventional chemotherapy schedule in those with low endocrine activity (HR 0.37, 95% CI: 0.26–0.54) but not in those with high activity (HR 0.95, 95% CI: 0.62–1.47). Unlike the PANTHER trial, which included both node-positive and node-negative patients, C9741 focused on node-positive cases and evaluated doxorubicin, cyclophosphamide, and paclitaxel in dose-dense versus conventional schedules, incorporating biomarker analysis. These findings challenge the use of clinicopathological features alone for selecting dose-dense chemotherapy and highlight the importance of endocrine activity in treatment decisions.

In addition, previous studies on adjuvant dose-dense chemotherapy in breast cancer were characterised by certain limitations that have been addressed by the PANTHER trial. The Cancer and Leukemia Group B 9741 and the Gruppo Italiano Mammella 2 trials (18,19), compared sequential anthracyclines and taxanes administered every 3 weeks versus every 2 weeks. While the patients in these trials had similar histopathological characteristics to those in the PANTHER trial, the PANTHER trial used docetaxel once every 3 weeks, while the other trials used paclitaxel once every 3 weeks. The E1199 trial, which compared docetaxel versus paclitaxel once every 3 weeks, showed that docetaxel was associated with improved disease-free and OS compared to paclitaxel (20). A trial-level meta-analysis showed that cumulative dose and dose-dense schedules were associated with improved outcomes compared to the standard of care treatment only when paclitaxel once every 3 weeks was used as the comparator group (4). These studies suggest

that the positive results observed in previous dose-dense chemotherapy trials may be attributed to the less effective control regimen (paclitaxel once every 3 weeks) rather than a true advantage of the dose-dense schedule.

Other trials that explored the impact of dose-dense anthracycline treatment, such as the EORTC-NCIC-SAKK multicenter study (21) and the MIG-1 study (18), did not show improved outcomes. It's important to note that the SAKK and MIH-1 trials used an anthracycline dose of 60 mg/m^2, which is now considered suboptimal, in the context of FEC regimen without using sequential taxane chemotherapy, whereas the UKTACT2 trial used an anthracycline dose of 100 mg/m^2 followed by either CMF or capecitabine chemotherapy. One exception is a study by Burnell *et al.*, which did demonstrate improved relapse-free survival when using a dose-dense schedule (22). Specifically, EC given 2-weekly with an epirubicin dose of 120 mg/m^2 followed by weekly paclitaxel was superior to 3 weekly AC/T with a doxorubicin dose of 60 mg/m^2. This trial also suggests that the improved outcomes observed in the EBCTCG meta-analysis may not be solely due to a weaker control regimen, as previously suggested (4) but also due to the absence of adjuvant taxane chemotherapy.

The GIM2 and PANTHER trials, with long-term follow-up, refine the optimal use of dose-dense chemotherapy in EHRBC (1,23,24). GIM2 trial data support that the optimal adjuvant chemotherapy for EHRBC should not include fluorouracil (23). Ideal candidates include node-positive patients, where significant disease-free and OS improvements are observed, irrespective of body mass index (24). In hormone receptor-positive, HER2-negative subgroups, benefits are modulated by composite prognostic risk scores (CPRS), favouring medium to high-risk individuals based on the GIM2 trial (25). PANTHER's comparison to a docetaxel-containing regimen further validates dose-dense efficacy, suggesting inherent advantages beyond comparisons to suboptimal treatments (1).

Tailored approaches, using multiparametric risk assessments in hormone receptor-positive, HER2-negative disease, are crucial (25). While PANTHER's OS benefit was non-significant, it reinforces dose-dense efficacy, emphasizing the importance of recurrence data. Collectively, these trials refine, rather than alter, existing treatment paradigms, emphasizing individualized strategies based on risk, patient characteristics, and a comprehensive evaluation of recurrence and survival. Oncologists should thus prioritize dose-dense schedules in high-risk early breast cancer and engage in informed patient discussions and an individualized approach.

In conclusion, the PANTHER trial is the first to demonstrate an improvement in clinical outcomes with the use of dose-dense chemotherapy compared to standard adjuvant chemotherapy using the optimal taxane schedule. It confirms that docetaxel every 3 weeks is the standard of care and shows the superiority of a dose-dense schedule. This trial also addressed the limitations of previous studies by comparing a dose-dense schedule to a control group receiving docetaxel once every 3 weeks, which is considered the optimal standard of care. This strengthens the evidence supporting dose-dense adjuvant chemotherapy as a superior treatment strategy for high-risk early breast cancer, provided that additional toxicities can be tolerated and managed. However, the approval of targeted treatments, along with the increasing use of neoadjuvant chemotherapy with antibody therapy in high-risk TNBC and HER2-positive breast cancer, underscores the importance of stratifying clinically high-risk patients using genomic tests or biomarkers such as Ki67 endocrine response (17). This stratification should guide the use of adjuvant dose-dense chemotherapy in populations at high risk of relapse, while carefully considering the risk of developing acute or long-term toxicities. Therefore, further research is essential to identify genomic and molecular features of patients who would most benefit from the dose-dense chemotherapy approach.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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